

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-942

CORRESPONDENCE



Food and Drug Administration
Rockville MD 20857

JUL 20 1998

NDA 18-654 Versed (midazolam)
NDA 20-942 Versed (midazolam)

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110 -1199

Attn: Margaret Jack
Program Director, Drug Regulatory Affairs

Dear Ms. Jack:

To obtain needed pediatric information on Versed® (midazolam) syrup, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A(a) of the Federal Food, Drug, and Cosmetic Act (the Act). FDA requests that you submit information from the following:

Types of studies:

Study 1: Single dose, pharmacokinetic/pharmacodynamic study comparing at least three dosage levels of midazolam syrup in patients between the ages of 6 months and 16 years who require sedation for minor procedures.

Study 2: Actual use study, or any other controlled clinical trial, that meets existing GLP and GLC standards, comparing at least three dosage levels of midazolam syrup in children between the ages of 6 months and 16 years undergoing sedation prior to surgical or diagnostic procedures using general anesthesia with mask induction.

Submit all other relevant safety information that is available.

Objective/rationale:

Study 1: Assess the pharmacokinetics of oral midazolam in the pediatric population and obtain preliminary data on the relationship between plasma concentrations of midazolam and sedation scores. Use this data to determine an optimal dosage range for this population and to assess safety in the targeted population.

Study 2: Assess the efficacy and safety of oral midazolam in the pediatric population.

Indication to be studied: Sedation/anxiolysis and amnesia prior to diagnostic/therapeutic or endoscopic procedures or before induction of anesthesia.

NDA 18-654

NDA 20-942

Page 2

Study design:

Study 1: Dose-ranging pharmacokinetic/pharmacodynamic study evaluating at least three different doses of midazolam syrup.

Study 2: Randomized, double blind, dose-response trial comparing at least three different doses of midazolam syrup.

Age group in which studies will be performed: Children between the ages of 6 months and 16 years. Studies should be stratified to three age ranges as appropriate to determine age-dependent pharmacokinetics.

Number of patients to be studied or power of study to be achieved:

Study 1: To determine dose proportionality, a sample size sufficient to detect a difference of 2.0 standard deviations between any two oral doses, with a power of 80% and an alpha level of 0.05.

Study 2: Sufficient size to detect a difference in efficacy and/or safety between the highest and lowest doses studied.

Entry criteria: (i.e., inclusion/exclusion criteria):

Study 1: Pediatric patients, physical status American Society of Anesthesiologists (ASA) Classification I, II or III, who require minor in-hospital or day-stay procedures.

Study 2: Pediatric patients, physical status ASA Classification I, II or III, who require sedation prior to surgical or diagnostic procedures requiring general anesthesia with mask induction.

Clinical endpoints, if appropriate:

Study 1: Determination of plasma concentrations of oral midazolam and the relationship of those concentrations to clinical sedation and formulation of dosing recommendations based upon the data obtained.

Study 2: Determination of the adequacy of sedation and anxiolysis, as well as the safety profile, of various doses of oral midazolam when administered to patients in the population described above.

Study evaluations:

Study 1: Pharmacokinetic data, sedation levels, and safety data.

Study 2: Adequacy of sedation by dose and safety data by dose.

NDA 18-654

NDA 20-942

Page 3

Drug information:

- * ***Dosage form:*** syrup
- * ***Route of administration:*** oral
- * ***Regimen:*** single dose
- * ***Formulation:*** as appropriate for dosage form and pediatric population

Safety concerns: Respiratory depression, airway obstruction, emesis and aspiration, and paradoxical CNS events should be carefully examined and reported, along with any adverse events occurring with a dose related frequency.

Statistical information (statistical analyses of the data to be performed):

Study 1: Descriptive analysis of the pharmacokinetic parameters and comparison of the dose normalized pharmacokinetic parameters between the dose groups.

Study 2: Comparison of the rates of satisfactory sedation between the dose groups and descriptive analyses of adverse events.

Labeling that may result from the studies: Information allowing the proper dose for safe and effective use in pediatric patients for the indications noted above.

Format of reports to be submitted: Full study reports or analyses addressing the issues outlined in this request with full analysis, assessment, and interpretation. Include other information as appropriate.

Timeframe for submitting reports of the studies: On or before July 30, 1998.

Reports of these studies should be submitted as a supplement to your approved NDA, as an NDA, or as an amendment to your pending application with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports of these pediatric studies, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

NDA 18-654
NDA 20-942
Page 4

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact David Morgan, Project Manager, at (301) 443-3741.

Sincerely yours,



Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

MORGAN

Food and Drug Administration
Rockville MD 20857

JUN 4 1998

NDA 20-942

Hoffmann-La Roche, Inc.
340 Kingsland Street
Nutley, New Jersey 07110

Attention: Betty C. Holland, M.S.
Program Director, Drug Regulatory Affairs

Dear Ms. Holland:

Please refer to your pending February 4, 1998 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Versed (midazolam hydrochloride) Syrup 2 mg/mL Oral.

We also refer to your amendments dated March 04, and April 30, 1998.

In reference to the teleconference between you and representatives of our Chemistry Section on June 1, 1998 the following deficiencies are being submitted.

To complete our review of the Chemistry section of your submission, we request the following:

With regard to the drug substance:

1. Please submit information on the proof of structure of midazolam. This information could not be located in NDA 18-654,
2. Please clarify if the preparation of the reference standard differs from that of the bulk drug substance?
3. Clarify why the Certificate of Analysis for the Reference Standard (Vol. 5, page 221) does not show testing for the residual solvents

4. It was noted in NDA 18-654 that the validated Method for residual solvents of the drug substance tested for the presence of Your currently submitted specification sheet for testing the drug substance is testing for such solvents as please explain.
5. Please indicate in which step of the synthesis of midazolam
6. During the synthesis of midazolam, it was noted that in-process testing involved analysis. Were any of the impurities and residual solvents detected in the testing of the drug substance?
7. Submit the photographs or cartoons of the and identify the R_f positions of midazolam, Ro 21-5344, Ro 21-5561, Ro 21-5751 and the unspecified impurities from the drug substance lots 92003, 950025, and 960029.
8. Revise the Test and Specification sheet for the drug substance to include specification limits showing: Total Specified and Unspecified Impurities.
9. Submit any currently available stability data for lots 950025, 920003, and 960029.

With regard to the drug product:

10. It is noted that the impurity Ro- 21-5344 has a retention time very close to midazolam, minutes and minutes respectively. What assurance is there that the midazolam peak is not contaminated?
11. It is recommended that the following tests be included in the Tests and Specifications of the drug product:

- a precipitation test in the Appearance Test
 - a viscosity test in the release and stability testing protocol.
 - a deliverable volume test (as per USP 23 (698) page 1790) including data showing that the syringe can deliver all of the doses.
12. Revise the Tests and Specifications for the drug product per ICH Q3B guidance by including each specified impurity and unspecified impurity and total degradation products.
13. The stability protocol should be revised as follows:
- a) Perform initial testing at each storage condition.
 - b) Perform testing at one and three months under the following storage conditions.
 - 2°C- % RH
 - C- % RH
 - c) Perform testing at one and six months in a light chamber.
14. It was noted that the product was manufactured under
- the _____ has been recorded, and that
Syrup and stored for _____ was filled with the _____ mg/mL
_____ hours under _____
What evidence has been recorded to
indicate that light will affect or not affect the
product when stored up to the proposed 18 months
expiration date?
15. Submit an update on all available stability data on the following batches: AP-26184-016, AP-26184-017 and AP-26184-018.

16. Please explain your batch numbering system and your sampling plan for accepting or rejecting a batch.
17. How is the product tested to ensure that there is no spillage when the syringe is inserted into the opening of the press-in cap and the bottle is inverted to withdraw the syrup. We recommend that you institute a test and specification to insure that spillage does not occur.
18. Submit the data from the functionality test which indicated the accuracy in volume delivery of Dispenser.
19. Submit evidence showing how the structures were determined for the impurities Ro 27-3136 and Ro 27-5272.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact David Morgan, Project Manager, at (301) 443-3741.

Sincerely,

/s/ *MD*
Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-942

Page 5

cc:

Original NDA 20-942

HFD-170/Div. Files

HFD-170/CSO/DMorgan/CMOODY

HFD-170/JROSS/ADSA(6-2-98)

HFD-170/BRAPPAPORT/CMcCormick

HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: DM/June 1, 1998/20942.chem

Initialed by:

final:

INFORMATION REQUEST (IR)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 1 1998

NDA 20-942

Hoffmann-LaRoche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Attention: Margaret Jack
Program Director
Drug Regulatory Affairs

Dear Mrs. Jack:

Please refer to your pending February 4, 1998 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VERSED (midazolam hydrochloride) Syrup 2mg/ml.

As discussed by telephone on March 20, 1998 between Margaret Jack, Program Director and David Morgan, Project Manager of this Division the following information was requested.

To complete our review of the Abuse Liability, and Pharmacology, sections of your submission, please submit the following:

Abuse Liability Package

Per 21 CFR 314.50(5)(vii) when a NDA application is submitted for a drug that has a potential for abuse, the sponsor must submit an abuse liability package with the NDA submission. This package must contain a description and analysis of studies or information related to abuse of the drug and scheduling proposal. In compliance with this regulation, you should submit the following information:

1. All preclinical data (i.e., sponsor's studies and published literature) relevant to the abuse potential of midazolam.
2. All clinical data (i.e., sponsor's studies and published literature) relevant to the abuse potential of midazolam.
3. Worldwide epidemiology data concerning abuse of injectable and oral formulation of midazolam.

Risk Management Plan

The agency has requested that sponsors with similar applications develop a Risk Management Program which address drug diversion, prevention of off-label use, and drug accountability. The agency would like you to address the following points:

1. How will you ensure that the drug will only be used in the proposed "setting"?
2. What steps will be taken to prevent diversion of this product?
3. Will your drug product only be advertised in anesthetic community?
4. How will you ensure no off-label use?
5. In the event that this product is highly desirable for abuse, would you consider reformulating so that the drug is not overly appealing?
6. Describe the mechanism you are proposing for your record keeping of this product.
7. Will there be limitations on the container size?
8. What steps will be taken to minimize the risk of drug overdose with your product?
For example,
 - a. Educational Programs (submit outline of plan)
 - b. Will this product be restricted for use to specific health care providers?

Pharmacology:

Regarding the study entitled, "Midazolam Syrup (Ro21-3981): An acute (single Dose) Oral (Intubation) Toxicity Study in Two -Week Observation period (Study No. 06827). Research Report No. N-138782",

Please provide the individual animal data for the clinical observation (including severity, onset and duration) and deaths (including time after drug administration), by treatment and sex.

NDA 20-492

Page 3

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact David Morgan, Project Manager, at (301) 443-3741.

Sincerely,

/s/

McD

Cynthia G. McCormick, M.D.

Director

Division of Anesthetic, Critical Care, and

Addiction Drug Products, HFD-170

Office of Drug Evaluation III

Center for Drug Evaluation and Research

NDA 20-492
Page 4

cc:

Original NDA 20-492
HFD-170/Div. Files
HFD-170/CSO/DMorgan
HFD-170/BHayes/KHaberny

Drafted by: /May 20, 1998/20492.adv
Initialed by: CPMOODY 5-20-98
final:

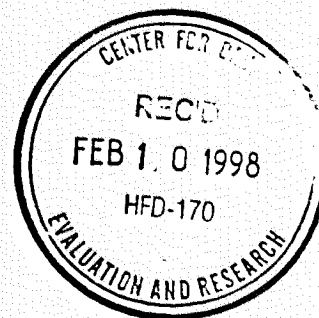
INFORMATION REQUEST (IR)

20492
HFD.

Roche

January 2, 1998

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, Pennsylvania 15259-0001



Ladies and Gentlemen:

**RE: NDA 20-942 - VERSED® (midazolam HCl) Syrup
HUMAN DRUG APPLICATION FEE - I.D. No. 3366**

Enclosed please find a check in the amount of _____ made payable to the U.S. Food and Drug Administration. This payment represents the user fee required for our Original New Drug Application for VERSED (midazolam HCl) Syrup dated January 12, 1998.

If you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Elisa Scordato Mandra

Elisa Scordato Mandra
Associate, Labeling
Drug Regulatory Affairs
(973) 562-3683 (telephone)
(973) 562-3700/3554 (fax)

Mar 2

ESM:eh

Enclosure: Check No. 01264284

HLR No. 1998-1

Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

20942

APPLICANT INFORMATION

NAME OF APPLICANT Hoffmann-La Roche Inc.	DATE OF SUBMISSION February 4, 1998
TELEPHONE NO. (Include Area Code) (973) 562-3724	FACSIMILE (FAX) Number (Include Area Code) (973) 562-3700
APPLICANT ADDRESS (Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued): 340 Kingsland Street Nutley, New Jersey 07110-1199	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, Zip Code, telephone & FAX Number) IF APPLICABLE Thomas Watson Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) midazolam hydrochloride	PROPRIETARY NAME (trade name) IF ANY VERSED
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (if any) Ro 21-3981
DOSAGE FORM: Syrup	STRENGTHS: 2 mg/mL
ROUTE OF ADMINISTRATION: Oral	

(PROPOSED) INDICATION(S) FOR USE:

Sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedure or before induction of anesthesia in pediatric patients

APPLICATION INFORMATION

APPLICATION TYPE (check one)	
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2) <input type="checkbox"/> 507	
IF AN ANDA, or AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION	
Name of Drug	Holder of Approved Application
TYPE OF SUBMISSION (check one)	
<input checked="" type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO PENDING APPLICATION
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT
<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
<input type="checkbox"/> OTHER	<input type="checkbox"/> SUPPLY SUPPLEMENT

REASON FOR SUBMISSION

Original New Drug Application

PROPOSED MARKETING STATUS (Check one) ☒ Prescription Product (Rx) ☐ Over-The-Counter Product (OTC)

NUMBER OF VOLUMES SUBMITTED 67 THIS APPLICATION IS ☒ Paper ☐ Paper & Electronic ☐ Electronic

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND and NDA 18-654

This application contains the following items: (check all that apply)

X	1. Index
X	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing and controls information (e.g. 21 CFR 314.50 (d)(1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k) (1))
X	17. Field copy certification (21 CFR 314.5 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. Other (Specify)


CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substance Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision. The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT



TYPED NAME AND TITLE

Thomas J. Watson
Program Director, DRA

DATE

2/4/98

ADDRESS (Street, City, State, and ZIP Code)

340 Kingsland Street
Nutley, New Jersey 07110-1199

Telephone Number

(973) 562-3724

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.



Pharmaceuticals

February 3, 1998

Ms. Regina Brown
Pre-Approval Program Manager
Food and Drug Administration
120 North Central Drive
North Brunswick, NJ 08902

Re: **NDA 20-942 - VERSED® (midazolam HCl) Syrup**
Original New Drug Application

Dear Ms. Brown:

In accordance with 21 CFR 314.50 (k)(3), we hereby forward to you a field copy of the Section 3 (Application Summary) and Section 4 (Chemistry, Manufacturing and Control Portion) of the Original New Drug Application) for VERSED (midazolam HCl) Syrup, NDA 20-942.

I hereby certify that this copy is identical in all respects to that provided to the Center in Rockville, MD.

Sincerely,

HOFFMANN-LA ROCHE INC.

Betty C. Holland, M.S.
Program Director
Drug Regulatory Affairs
(973) 562-5549 (phone)
(973) 562-3700 (fax)

BCH/TN
Attachments
HLR No. 1998-315

August 4, 1998

Food and Drug Administration
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170
Center for Drug Evaluation and Research
DOCUMENT CONTROL ROOM 9B-23
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857



NEW CORRESP

Ladies and Gentlemen:

RE: NDA 20-942 VERSED® (midazolam HCl) Syrup
Market Exclusivity Information

Reference is made to Hoffmann-La Roche Inc.'s NDA 20-942 dated February 4, 1998. Pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act, the following Market Exclusivity Information supplements exclusivity information provided with the NDA and is submitted for inclusion in the above-noted NDA.

Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

Additionally, as required, two copies of this information are also being submitted to the Central Document Room.

Should you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely yours,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack
Program Director
Drug Regulatory Affairs
Phone: (973) 235-4463
Fax: (973) 562-3700/3554

HLR No. 1998-1951



AMENDMENT
Su

July 17, 1998

Food and Drug Administration
Division Anesthetic, Critical Care and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857-1706

Ladies and Gentlemen:



Re: **NDA 20-942 VERSED® (midazolam HCl) Syrup**
Four Month Safety Update

We are herewith notifying the Agency that there is no additional safety information available which is applicable to this application and are confirming that all available information has been previously provided to the Agency regarding this application.

If you have any questions concerning this application, please contact the undersigned at the numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret Jack

Margaret Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (phone)
(973) 562-3700 (fax)

MJJ:EMD
HLR No. 1998-1809

DUPLICATE